#TPS3108: Phase I STORM study (KEYNOTE 200): Intravenous delivery of a novel oncolytic therapy agent, Coxsackievirus A21 in combination with pembrolizumab in advanced cancer patients.

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Background
Coxsackievirus A21 (CVa21, CVa21AK) is a naturally occurring ICAM-1 targeted oncolytic immunotherapeutic virus. Intravenous (IV) delivery of CVa21 targets various systemic solid tumors (Figure 1). Tumor infection by CVa21 can increase levels immune-checkpoint molecules, immune-cell infiltration and enhancement of systemic antitumor immune response. Pembrolizumab is a human programmed death receptor-1 (PD-1) IgG-like antibody that has yielded significant solid tumor responses via reversion of tumor induced T-cell suppression. Preclinical studies in an immune-compromised Non-Small Cell Lung Cancer (NSCLC) confirmed that combinations of IV CVa21 + anti-PD-1 mAbs mediated survival benefit compared to use of either agent alone (Figure 2). We postulate that the combination of CVa21 pembrolizumab may translate to a similar benefit in the clinic. We describe a Phase I study assessing safety and efficacy of IV CVa21 ± pembrolizumab in advanced cancer patients.

Key Inclusion criteria
- Active cancer disease: untreated or recurrent within last 3 months, metsurgical operation within 6 months, concomitant heart failure = class II, cardiac ventricular arrhythmies requiring anti-arrhythmic therapy.
- Symptomatic, or expecting to convalesce or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Known history of Human Immunodeficiency Virus (HIV 1/2 antibodies), known active Hepatitis B (e.g. HBV DNA reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- Known primary or second malignancy that would interfere with the conduct of the study.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include baseline cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative surgery or in situ cervical cancer.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer and/or anti-malignancy within 21 days prior to study Day 1 or has not recovered (i.e. ≥ Grade 3) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

Key Exclusion criteria
- Active cardiac disease: unstable angina or onset of angina within last 3 months, myocardial infarction within 6 months, congestive heart failure = class II, cardiac ventricular arrhythmies requiring anti-arrhythmic therapy.
- Symptomatic, or expecting to convalesce or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
- Known history of Human Immunodeficiency Virus (HIV 1/2 antibodies), known active Hepatitis B (e.g. HBV DNA reactive) or Hepatitis C (e.g. HCV RNA [qualitative] is detected).
- Known primary or second malignancy that would interfere with the conduct of the study.
- Known additional malignancy that is progressing or requires active treatment. Exceptions include baseline cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative surgery or in situ cervical cancer.
- Active infection requiring systemic therapy.
- Has had prior anti-cancer and/or anti-malignancy within 21 days prior to study Day 1 or has not recovered (i.e. ≥ Grade 3) from adverse events due to agents administered more than 21 days earlier.
- Has known active central nervous system metastases and/or carcinomatous meningitis.

Study Objectives

Primary Objectives
Part A: To determine if CVa21 given intravenously is capable of tracking to malignant tumours.
- To establish a safe dose schedule of CVa21 to take into subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVa21.

Part B: To assess the safety and efficacy of intravenous CVa21 and intravenous pembrolizumab in solid tumours of metastatic head and neck and non small-cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVa21 in combination with intravenous pembrolizumab.
- To investigate if pembrolizumab in combination with intravenous pembrolizumab is capable of redirecting to remote tumour sites by exhibiting CVa21 RNA in metastatic lesions at biopsy.
- To determine if CVa21 in combination with intravenous pembrolizumab is capable of replicating in the tracked tumour sites leading to tumour cell lysis while sparing the surrounding normal cells.

Secondary Objectives
Part B
- To assess efficacy via RECIST 1.1 and immune-related RECIST (RECED) criteria.
- To correlate ICAM-1 expression and CAF expression with the ability of CVa21 to reach target and replicate within tumour cells.
- To assess immune response (e.g. immune cell infiltrates) after the first course of CVa21 via biopsy of an accessible lesion tumor.
- To correlate ICAM-1 expressivity and DAF expressivity with the ability of CVa21 to reach its target and replicate within tumour sites leading to tumour cell lysis.
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- To correlate ICAM-1 expressivity and DAF expressivity with the ability of CVa21 to reach its target and replicate within tumour sites leading to tumour cell lysis.

Part A
- To describe the safety profile for intravenously-administered CVa21.
- To assess tolerance to intravenous CVa21 for up to 8 courses (21 day cycle) in combination with pembrolizumab.
- To assess immune response (e.g. immune cell infiltrates) after the first course of CVa21 via biopsy of an accessible lesion tumor.
- To correlate ICAM-1 expressivity and DAF expressivity with the ability of CVa21 to reach its target and replicate within tumour sites leading to tumour cell lysis.

To determine if CVa21 given intravenously is capable of tracking to malignant tumours.
- To establish a safe dose schedule of CVa21 to take into subsequent Phase 2 clinical trials.
- To describe the safety profile for intravenously-administered CVa21.

Part B
- To assess the safety and efficacy of intravenous CVa21 and intravenous pembrolizumab in solid tumours of metastatic head and neck and non small-cell lung cancer.
- To identify a safe and potentially effective Phase 2 dose for CVa21 in combination with intravenous pembrolizumab.
- To investigate if pembrolizumab in combination with intravenous pembrolizumab is capable of redirecting to remote tumour sites by exhibiting CVa21 RNA in metastatic lesions at biopsy.
- To determine if CVa21 in combination with intravenous pembrolizumab is capable of replicating in the tracked tumour sites leading to tumour cell lysis while sparing the surrounding normal cells.

Eligibility Criteria

Part A: Patients are infused with CVa21 in 100 mL saline at Cohort 1 (n = 3), at a dose of 1 x 10⁸ TCID₅₀ in Cohort 2 (n = 3) at a dose of 3 x 10⁸ TCID₅₀ and in Cohort 3 (n = 12-18) at a dose of 1 x 10⁹ TCID₅₀ on study days 1,3,5,22 and Q3W for 6 additional infusions. Part A enrolment is almost complete.

Part B: Patients are infused with CVa21 in 100 mL saline ± pembrolizumab. In Cohort 1 (n = 3), CVa21 is administered at a dose of 1 x 10⁸ TCID₅₀ in Cohort 2 (n = 3) at a dose of 3 x 10⁸ TCID₅₀ and in Cohort 3 (n = 48) at a dose of 1 x 10⁹ TCID₅₀ on study days 1,3,5,22,29 and Q3W for 8 additional infusions. Pembrolizumab is given in intravenous 200 mg Q2W from Day 8 up to 2 years. Treatment with CVa21 ± pembrolizumab will continue until confirmed CR or PD (whichever comes first) per RECIST or DLT.

Study Design

Study Treatment

Part A: Cohort 1: 3 patients, Cohort 2: 3 patients, Cohort 3: 12-18 patients. Each cohort does one 21 day cycle. Part A (with advanced metastases following 2 achievement infections of CVa21 (WT/HDVinfected)).

Part B: Cohort 1: 3 patients, Cohort 2: 3 patients, Cohort 3: 12-18 patients. Each cohort does one 21 day cycle. Part B (with advanced metastases following 2 achievement infections of CVa21 (WT/HDVinfected)).

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